



Editorial

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Steroid-refractory Chronic Graft-versus-Host Disease

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Abstract

Steroid-refractory graft versus host disease (SR-GVHD) presents a particularly challenging clinical problem. The mechanisms underlying steroid resistance remain incompletely understood but involve complex interactions between donor T cells, host antigen-presenting cells, and dysregulated inflammatory pathways. SR-GVHD is associated with significantly increased morbidity and mortality, with overall survival rates declining substantially in this population. Treatment strategies are increasingly individualized based on disease severity, organ involvement, and donor-recipient factors.

Keywords: Steroid-refractory; Chronic graft versus host disease; FDA approved; Belumosudil; Protein Kinase

Abbreviations: SR-cGVHD: Steroid-Refractory cGVHD; FDA: Food and Drug Administration; ROCK2: rho-Associated Coiled-Coil-Containing Protein Kinase-2; ORR: Overall Response Rate; CSF-1R: Colony Stimulating Factor-1 Receptor

Introduction

Chronic graft versus host disease (cGVHD) affects up to 50% of transplant recipients, with increased incidence over recent years. Risk factors include peripheral blood stem cell grafts, donor lymphocyte infusion, lack of T-cell depletion, female donor to male recipient transplants, HLA disparity, older age, and CMV seropositivity. Higher risk in unrelated donor-recipient pairs and with certain disease types like leukemia [1].

Pathogenesis of cGVHD

- The pathogenesis of cGVHD is not well understood. It is a complex and multifactorial condition. T and B cells as well as innate responses, including the transition from inflammation to fibrosis involving fibroblasts and macrophages are involved.
- Decreased regulatory T cells (CD4 + CD25 +) have been observed in cGVHD.
- Auto-antibody production by host-reactive B cells and plasmablasts, fibrotic changes following type 2 donor responses, and thymic damage impairing immune-reconstitution.
- Increased levels of transforming growth factor- β are observed in cGVHD patients compared to healthy controls, although its role in disease pathogenesis has not been established.

There is also an emerging understanding of the role of gut microbiome on cGVHD presentation. Loss of flora diversity following allo-HSCT has been associated with the development of aGVHD and cGVHD, as well as increased mortality risk [2].

Current Treatment Strategies

- First-line treatment is systemic steroids with or without calcineurin inhibitors. Up to 70% of patients are steroid-refractory or dependent and require second or third-line therapies [1].
- SR-cGVHD has been defined as cGVHD progression at ≥ 1 mg/kg/day prednisone for 1–2 weeks, or stable cGVHD on ≥ 0.5 mg/kg/day prednisone for 1–2 months. Additional patients remain steroid-dependent with repeated symptom flares during taper of corticosteroids below 0.25 mg/kg/day. SR-cGVHD is associated with significantly increased morbidity and mortality [2].
- Long-term immunosuppressants pose toxicity and infection risks [1].
- An increasing number of treatment options are becoming available. There are no standard second-line treatments for SR-cGVHD patients. Data are limited, and no consensus has been found on an optimal approach [2].

Food and Drug Administration (FDA)-approved therapies for cGVHD

The following drugs were approved by FDA for cGVHD: Ibrutinib was approved in August 2017 after failure of ≥ 1 lines of systemic therapy in adults, ruxolitinib was approved in September 2021, after failure of 1 or 2 lines of systemic therapy for cGVHD in adult and pediatric patients aged ≥ 12 years and Belumosudil was approved in July 2021 for adult and pediatric patients aged ≥ 12 years after failure of at least 2 prior lines of systemic therapy. Axatilimab-csfr was approved by FDA in August 2024 [3].

Ibrutinib

Ibrutinib targets buton tyrosine kinase pathway in B cells and blocks downstream signaling from the B-cell receptor. Ibrutinib also inhibits interleukin-2 (IL-2)-inducible T cell kinase (ITK) in T cells. The recommended dose of ibrutinib for adult patients with cGVHD is 420 mg orally once daily, and 240 mg/m² by mouth daily for pediatric patients aged 1 to less than 12 years. Adverse effects are mainly grade 1 or 2. The most common grade ≥ 3 adverse effects are pneumonia, fatigue, and diarrhea. Continuous responses for at least 44 weeks were reported in 55% of responders [3].

Ruxolitinib

Ruxolitinib interferes with JAK 1 and 2 activations, which reduces signaling of multiple cytokine receptors. Ruxolitinib treatment reduced collagen deposition in the lungs and improved pulmonary function in a murine model of cGVHD. Comparison of ruxolitinib versus the best available therapy (BAT) in corticosteroid-refractory and corticosteroid-dependent cGVHD patients showed greater overall response rate (ORR) and modified Lee symptom score response at week 24 in the ruxolitinib group compared with the control group. The median failure-free survival was longer in the ruxolitinib group compared with the control group (REACH-3, NCT03112603). Real-world studies support the observed results of the clinical trial. The recommended dose of ruxolitinib is 10 mg oral twice daily, after failure of 1 or 2 lines of systemic therapy for cGVHD in adult and pediatric patients aged ≥ 12 years [3].

Belumosudil

Belumosudil is an oral selective inhibitor of rho-associated coiled-coil-containing protein kinase-2 (ROCK2) that blocks downstream activity of multiple cytokine and growth factor receptors and integrins and proinflammatory NF- κ B signaling. Belumosudil inhibits STAT3 activation and IL-21, IL-17, and interferon gamma production, which play central roles in cGVHD pathogenesis. A best ORR was 74% - 77% to 200 mg daily and 200 mg twice daily belumosudil. The failure-free survival was 56% at 12 months, and 59% had a clinically meaningful improvement in symptoms in the 200-mg daily approved dose (NCT03640481). The approved dose of belumosudil is 200 mg oral daily, for adult and pediatric patients aged ≥ 12 years with cGVHD after failure of at least 2 prior lines of systemic therapy [3].

Axatilimab

Axatilimab is an IgG4 monoclonal antibody with a high affinity for colony stimulating factor-1 receptor (CSF-1R) that depletes macrophages. An ORR of 74% with axatilimab at 0.3 mg/kg once every 2 weeks, was reported in refractory cGVHD patients (NCT04710576). A clinically significant decrease in symptoms was reported in 60% of the cohort receiving the approved dose. The approved dose of axatilimab-csfr was 0.3 mg/kg IV Q2W, after failure of at least 2 prior lines of systemic therapy of cGVHD in adult and pediatric patients weighing at least 40 kg [3].

Non-FDA approved therapies for steroid-refractory cGVHD

- Several non-FDA approved therapies may be considered for steroid-refractory cGVHD, when FDA-approved drugs fail or are unavailable. They include extracorporeal photopheresis (ECP), tyrosine kinase inhibitors like imatinib, investigational JAK/ROCK inhibitors such as rovadicitinib, and experimental cell-based therapies. Other options include abatacept, alemtuzumab, low-dose methotrexate, rituximab, and various immunosuppressants, with varying evidence and response rates.

Organ-specific efficacy

- Extracorporeal Photopheresis (ECP): immunomodulatory; 64% overall response; 29% complete response; effective for skin, oral, liver cGVHD.
- Imatinib: tyrosine kinase inhibitor; 79% response in small studies; 84% 18-month survival; targets fibrosis pathways.
- Cell therapies (DSCs, mesenchymal stromal cells) are experimental but promising for severe refractory cases.

Risks and Limitations

- These are regionally approved (e.g., in Europe or China) but not FDA-approved in the U.S. Some therapies (e.g., rovadicitinib, DSCs) are only available in clinical trials or outside the U.S.
- Safety profile: ECP is very safe but less potent; imatinib carries risks of cytopenias and fluid retention.
- There is no standardized sequencing beyond FDA-approved agents; treatment choice depends on organ involvement and physician experience [4-5].

Future Directions in cGVHD Management

Advances made, but further research needed on diagnosis, etiology, and treatment.

- Focus on early diagnosis, staging, prevention, and preemptive therapy.
- Emphasis on severe forms involving skin, lungs, eyes, GI tract.

- Need to understand immunologic mechanisms, resistance to steroids, and disease progression.
- Goal to refine targeted therapies and identify responsive patient subgroups [6,7].

Conclusion

Further research into the immunobiology of SR-GVHD, exploration of novel therapeutic targets, and optimization of combination strategies are essential to improve survival rates and reduce treatment-related mortality. Ultimately, successful management of SR-GVHD will require integration of mechanistic understanding with evidence-based clinical practice, enabling clinicians to provide more effective and individualized care for transplant recipients facing this life-threatening complication.

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